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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,428	07/16/2003	Dieter Heindl	21329-US	8931

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EXAMINER

LU, FRANK WEI MIN

ART UNIT PAPER NUMBER

1634

DATE MAILED: 06/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/621,428

Applicant(s)

HEINDL ET AL.

Examiner

Frank W Lu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 April 2005.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 15-39 is/are pending in the application.
4a) Of the above claim(s) 15-17 and 24-31 is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 18-23, 32-34 and 36-39 is/are rejected.
7) ☒ Claim(s) 35 is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 16 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on April 6, 2005 has been entered. Claims 15-28 have been canceled and new claims 1-14 and 29-39 have been added in the amendment filed on April 6, 2005. Although applicant canceled claims 1-14 in preliminary amendment filed on July 6, 2003, there are no claims 1-14 in this instant application. According to rule 1.126, canceled claims 15-28 are renumbered as claims 1-14, claims 29-31 are renumbered as claims 15-17, and newly added claims 1-14 and 32-39 are renumbered as claims 18-39. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the response filed on April 6, 2005. Since newly submitted claims 24-31 are directed to a method for qualitative or quantitative detection of a nucleic acid sequence in a nucleic acid sample and a method for the determination of the melting profile of a hybrid which are drawn to the same subject matter and fall entirely within the scope of the non-selected methods recited in canceled claims 7-14, newly added method claims 24-31 are considered as an invention that is independent or distinct from the invention originally claimed. Since applicant has received an action on the merits for the originally presented invention, this invention has not been constructively elected by original presentation for prosecution on the merits. Furthermore, claims 18-22 are not a contribution over the prior art (see the rejection under 35 U.S.C 102 below). Accordingly, newly submitted claims 24-31 and claims 15-17 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Therefore, claims 18-23 and 32-39 will be examined.

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Claim Objections

2. Claims 20 and 35 are objected to because of the following informalities: "is carrying" in line 6 of the claims should be "further carries".
3. Claims 23 and 39 are objected to because of the following informalities: there should be a coma between "a nucleic acid amplification primer" and "a template dependent nucleic acid polymerase" in lines 3 and 4 of the claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 33, 36, 38, and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To the extent that the claimed composition/or methods are not described in the instant disclosure, claims 33, 36, 38, and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

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and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Newly added claim 33 requires that the same nucleotide of said first oligonucleotide carrying the donor fluorescent entity carries the nitroindole moiety and newly added claim 36 requires that the same nucleotide of the oligonucleotide carrying the FRET donor entity also carries the nitroindole moiety. Although the specification describes that an oligonucleotide carrying a FRET donor entity and a nitroindole moiety capable of quenching fluorescence of said FRET donor entity (e.g., see page 5 of the specification and Examples 2-4 in pages 11-14 of the specification), the specification fails to define or provide any disclosure to support that the same nucleotide of said first oligonucleotide carrying the donor fluorescent entity carries the nitroindole moiety as recited in claim 33 and the same nucleotide of the oligonucleotide carrying the FRET donor entity also carries the nitroindole moiety as recited in claim 36.

MPEP 2163.06 notes "If NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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7. Claims 34 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 34 and 37 recite the limitation “the second entity” in the claims. There is insufficient antecedent basis for this limitation in the claim because there is no “second entity” in claims 32 and 35. Please clarify.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 18-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Nazarenko *et al.*, (US Patent No. 5,866,336, published on February 2, 1999).

Regarding claim 18, since Nazarenko *et al.*, teach a upstream hairpin primer comprising a fluorescent dye FAM and a quencher (ie., DABCYL) (see column 38 and Figures 24A to G) and a reverse primer labeled with a fluorescent dye rhodamine (see column 35 and Figure 13A), and it is known that FAM is a suitable donor for rhodamine (see column 18), Nazarenko *et al.*, disclose that first oligonucleotide (ie., the upstream hairpin primer) carrying a FRET donor entity (ie., FAM) and at least one second entity (ie., the quencher), said second entity being a

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compound (ie., DABCYL) which is capable of quenching fluorescence emission of said donor fluorescent entity (ie., FAM) and a second oligonucleotide (ie., the reverse primer) carrying a FRET acceptor entity (ie., rhodamine) but not carrying a FRET donor entity as recited in claim 18.

Regarding claim 20, since Nazarenko *et al.*, teach a upstream hairpin primer comprising a fluorescent dye FAM and a quencher (ie., DABCYL), a downstream primer (see column 38 and Figures 2, 3, 24A to G) and a reverse primer labeled with a fluorescent dye rhodamine (see column 35 and Figure 13A), and it is known that FAM is a suitable donor for rhodamine (see column 18) and claim 20 does not require that the third oligonucleotide of claim 20 must be different from the second oligonucleotide of claim 18, Nazarenko *et al.*, disclose a first oligonucleotide and a second oligonucleotide (ie., the upstream hairpin primer and downstream primer) capable of acting as a pair of amplification primers for a template dependent nucleic acid amplification reaction, further characterized in that said first oligonucleotide (ie., the upstream hairpin primer) and a third oligonucleotide (ie., the reverse primer) are each labeled with one corresponding member of a FRET pair consisting of a FRET donor entity (ie., FAM) and a FRET acceptor entity (ie., rhodamine) wherein the oligonucleotide (ie., the upstream hairpin primer) carrying the FRET donor entity (ie., FAM) carries at least one second entity (ie., the quencher), said second entity being a compound (ie., DABCYL) which is capable of quenching fluorescence emission of said donor fluorescent entity (ie., FAM) and wherein the oligonucleotide (ie., the reverse primer) carrying the FRET acceptor entity (ie., rhodamine) does not carry a FRET donor entity as recited in claim 20.

Regarding claims 19 and 21, since Nazarenko *et al.*, teach that FAM connects DABCYL

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by A-hydrogen bond-T (see Figures 24A to G), Nazarenko *et al.*, disclose that the FRET donor entity (ie., FAM) and the second entity (ie., DABCYL) are carried on adjacent nucleotides of the first oligonucleotide (ie., the upstream hairpin primer) as recited in claims 19 and 21.

Regarding claim 22, since Nazarenko *et al.*, teach a template used for PCR PSA cDNA (see column 38) and all limitations recited in claim 18 or 20 (see above), Nazarenko *et al.*, disclose a composition comprising a nucleic acid sample (ie., a template used for PCR PSA cDNA) and a pair of hybridization probes (ie., the upstream hairpin primer and the reverse primer) according to claim 18 or a set of oligonucleotides (ie., the upstream hairpin primer, the downstream primer, and the reverse primer) according to claim 20 as recited in claim 22.

Therefore, Nazarenko *et al.*, teach all limitations recited in claims 18-22.

11. Claims 18, 19, 32, and 34 are rejected under 35 U.S.C. 102(e) as being anticipated by Frutos *et al.*, (US Patent No. 6,579,680 B2, priority date: February 28, 2000).

Regarding claim 18, since Frutos *et al.*, teach that a hybridized duplex formed by SEQ ID Nos: 3 and 4 comprising a fluorescent dye cy3, a quencher, and 5'-nitroindole (see column 7), Frutos *et al.*, disclose that first oligonucleotide (ie., the hybridized duplex formed by SEQ ID Nos: 3 and 4) carrying a FRET donor entity (ie., cy3) and at least one second entity (the quencher with a nitroindole), said second entity being a compound (ie., the quencher) which is capable of quenching fluorescence emission of said donor fluorescent entity (ie., Cy3) as recited in claim 18. Since Frutos *et al.*, teach an oligonucleotide labeled a fluorescent dye Rox (see column 10) and Rox can serve as an acceptor, Frutos *et al.*, disclose a second oligonucleotide

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(ie., the oligonucleotide labeled a fluorescent dye Rox) carrying a FRET acceptor entity (ie., Rox) but not carrying a FRET donor entity as recited in claim 18.

Regarding claim 32, since Frutos *et al.*, teach that a hybridized duplex formed by SEQ ID Nos: 3 and 4 comprising a fluorescent dye cy3, a quencher, and 5'-nitroindole (see column 7), Frutos *et al.*, disclose that first oligonucleotide (ie., the hybridized duplex formed by SEQ ID Nos: 3 and 4) carrying a FRET donor entity (ie., cy3) and a nitroindole moiety (SEQ ID NO: 4 labeled with a quencher with a nitroindole) capable of quenching fluorescence emission of said FRET donor entity (ie., Cy3) as recited in claim 32. Since Frutos *et al.*, teach an oligonucleotide labeled a fluorescent dye Rox (see column 10) and Rox can serve as an acceptor, Frutos *et al.*, disclose a second oligonucleotide (ie., an oligonucleotide labeled a fluorescent dye Rox) carrying a FRET acceptor entity (ie., Rox) as recited in claim 32.

Regarding claims 19 and 34, since Frutos *et al.*, teach that cy3 is located on 5' end of SEQ ID NO: 3 and the quencher (ie., dabcy1) is located on 3' end of SEQ ID NO: 4, and cy3 and the quencher is connected by G-hydrogen bond-C, Frutos *et al.*, disclose that the FRET donor entity (ie., cy3) and the second entity (ie., dabcy1) are carried on adjacent nucleotides of the first oligonucleotide (ie., the hybridized duplex formed by SEQ ID Nos: 3 and 4) as recited in claims 19 and 34.

Therefore, Frutos *et al.*, teach all limitations recited in claims 19, 20, 32, and 34.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko *et al.*, (1999) as applied to claims 18-22 above, and further in view of Stratagene catalog (page 39, 1988).

The teachings of Nazarenko *et al.*, have been summarized previously, *supra*. As shown the rejection under 35 U.S.C 102 (b), Nazarenko *et al.*, teach a pair of hybridization probes according to claim 18 or a set of oligonucleotides according to claim 20 as recited in claim 23. Since Nazarenko *et al.*, also teach a kit comprising a hairpin primer, a DNA polymerase and a buffer for PCR reaction (see columns 32 and 33), Nazarenko *et al.*, disclose at least one other component (ie., the DNA polymerase) as recited in claim 23.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine a pair of hybridization probes according to claim 18 or a set of oligonucleotides according to claim 20 and at least one other component such as a template dependent nucleic acid polymerase (ie., the DNA polymerase) taught by Nazarenko *et al.*, into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "[E]ach kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. 2) The other service provided in a kit is quality control" (page 39, column 1).

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

15. Claim 35 appears to be allowable if applicant can overcome above objection on claim 35 because the prior art in the record does not teach or suggest a set of 3 oligonucleotides comprising a first oligonucleotide and a second oligonucleotide capable of acting as a pair of amplification primers for a template dependent nucleic acid amplification reaction, further characterized in that said first oligonucleotide and a third oligonucleotide are each labeled with one corresponding member of a FRET pair consisting of a FRET donor entity and a FRET acceptor entity, wherein the oligonucleotide carrying the FRET donor entity further carries a nitroindole moiety capable of quenching fluorescence of said FRET donor entity.

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16. The patent from Frutos *et al.*, cannot used as a prior art to reject claim 35 since Frutos *et al.*, do not teach a first oligonucleotide and a second oligonucleotide capable of acting as a pair of amplification primers for a template dependent nucleic acid amplification reaction.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission.

17. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746.

The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
June 21, 2005



FRANK LU
PATENT EXAMINER